



The Management of Women with Bleeding Disorders

*Prepared by the Subcommittee on Women with Bleeding Disorders
for the Association of Hemophilia Clinic Directors of Canada (AHCDC)*

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Canadian Hemophilia Society
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Bleeding Disorders Initiative

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Introduction

Women with bleeding disorders often experience long-term disability during their child bearing years due to excessive menstrual bleeding. In fact, for the commonest bleeding disorder, von Willebrand disease (VWD), menorrhagia clearly represents the major disease-related morbidity^{1,2} and in rare instances, such as in the index case in the Aaland Islands, can result in a hemorrhagic death³.

Several recent studies have estimated the prevalence of menorrhagia to be between 59-93% in women with inherited bleeding disorders⁴⁻⁸. In comparison, approximately 10% of normal women experience menorrhagia. Another way of quantifying the clinical significance of this problem is to determine the number of women presenting to a physician with menorrhagia, who, on laboratory analysis, prove to have a definable bleeding disorder. This figure appears to be between 10-20%, with VWD comprising approximately 70% of cases and mild Factor XI deficiency being the next most frequently encountered problem⁹⁻¹¹.

In addition to the documentation of an increased prevalence of menorrhagia associated with bleeding disorders, there is also evidence that this complication significantly disrupts the quality of life of these women. Between 40-50% of women experiencing menorrhagia relate that they are limited in their activities and find working more difficult during their menstrual periods¹².

The purpose of this work is to provide for women with bleeding disorders suggestions on

- 1) the optimal management through multidisciplinary clinics,
- 2) the laboratory investigation of bleeding disorders,
- 3) the medical treatment of menorrhagia and
- 4) the management of pregnancy.

This work should not to be considered a complete review of the subject but rather a practical approach for physicians taking care of these patients. These suggestions represent the opinions of the Women with Bleeding Disorders Subcommittee of the Association of Hemophilia Clinic Directors of Canada (AHCDC) and is not an official recommendation from the AHCDC.

Multidisciplinary clinics for women with bleeding disorders

Menorrhagia accounts for 16% of gynecology referrals¹³: 10-20% of women with menorrhagia have an hereditary bleeding disorder and about 20% have a definable gynaecologic problem. A number of women will have both. The ideal approach in individual women is probably best achieved through a co-operative approach among the family physician, the gynecologist and the hematologist.

Objectives of multidisciplinary clinics

General objectives:

- To improve the quality of life of women with bleeding disorders.
- To create a forum for discussion between physicians and allied health professionals with different scientific backgrounds and expertise involved in the care of women with bleeding disorders.
- To advance knowledge in the area of bleeding disorders in women.
- To provide education for physicians, for patients and, ultimately for the general population.

Specific objectives:

- To provide adequate diagnostic workup for women with bleeding problems, and accurately identify underlying gynecological and hematological diseases.
- To provide adequate therapeutic interventions for bleeding problems; to reassess interventions in a timely fashion.
- To avoid unnecessary surgery.
- To avoid unnecessary use of blood products.
- To provide optimal preparation for anaesthesia, surgery, pregnancy, childbirth and the postpartum.
- To provide counselling and support.

Structure:

The team should have, as a minimum, a nurse, a hematologist and a gynecologist in the basic team required for clinical consultation. This team can meet with the patients, plan the diagnostic and therapeutic approach, and liaise with the family physician. Monthly or bimonthly clinics are probably ideal however, the frequency of the clinics can vary depending on the number of patients. These clinics can occur in the same or different locales.

The ideal multidisciplinary team has a broader representation of expertises, with a laboratory hematologist, an obstetrician-gynecologist, an anaesthetist, a family physician, a pharmacist, a laboratory technician and/or other interested health professionals. The core clinical team meets with patients as discussed above. The extended team meets regularly to discuss patients and standardise approaches. Ideally such an extended team should be able to contribute to education and the advancement of knowledge.

Designated secretarial support is essential.

Referral of patients:

The referral pattern will vary according to local expertise and should evolve with time. In some cases, patients will be referred by a gynecologist or family physician after exclusion of non-hematological causes of menorrhagia. In other cases, referral to the clinic will be the first step of investigation. In all cases, patients should be referred to the clinic by a physician.

Evaluation:

Before any coagulation investigation, patients should have a complete personal and family history and physical examination, including a gynaecological examination in most cases (not always necessary in adolescents). Complementary initial examinations should include a pelvic ultrasound, platelet count, hemoglobin/hematocrit, thyroid, renal and hepatic screen and prolactin level.

Women's own perceptions of their menstrual flow are often not reliable. This may be even more difficult if they compare themselves with other women of their family who may also have a coagulopathy. The definition of menorrhagia is the loss of greater than 80 ml of blood per menstrual cycle. The introduction of a graphical scoring system for menstrual bleeding has resulted in a more practical means of quantifying excessive bleeding¹⁴ (appendix 1). The pictorial blood assessment chart is easy for patients to use and has a sensitivity of 86% and specificity of 89%¹⁴. This can be sent to the patients for completion before their first visit to the clinic along with a questionnaire on their personal and familial bleeding history (appendix 2). Patients may not always need to be seen by both the gynecologist and the hematologist but can be oriented to one or the other depending on their special needs.

Training/CME:

Residents from family medicine, obstetrics-gynecology, internal medicine, and hematology training programs should rotate through the clinic. Specific objectives need to be formulated for each program. Family physicians could also attend some clinics as part of their CME if they identify this as a need.

Laboratory investigation of women with bleeding disorders

STEP I

Include screening tests that are usually performed during the initial investigation of menorrhagia

- Platelet count
- Hemoglobin/hematocrit

STEP II

Include laboratory investigation usually indicated in the following clinical situations:

1. No local cause for menorrhagia
2. Long-standing menorrhagia (present since menarche)
3. Menorrhagia causing anemia
4. Bleeding after hemostatic challenge (dental extraction, surgery or parturition)
5. Familial history of bleeding
 - Bleeding time/ closure time
 - Prothrombin time (PT)
 - Activated partial thromboplastin time (APTT)
 - Von Willebrand studies:
 - Factor VIII
 - VWF antigen
 - VWF functional assay
 - Multimer assay or crossed immuno-electrophoresis
 - Blood group
 - Factor VIII, FIX or FXI levels in patients with known familial deficiency

Step III

Further investigation as required

(e.g. positive history in the absence of VWD)

- Platelet function studies:
 - Platelet aggregation in response to ADP, epinephrine, collagen, arachidonic acid, ristocetin
- Coagulation factor levels to determine the basis of a prolonged APTT or PT
- Rare coagulation factor deficiencies that are not identified by screening tests (e.g. Factor XIII or α_2 antiplasmin)

Specialized studies determined by specific findings

- Genetic studies to identify specific mutations in potential and confirmed hemophilia carriers
 - Studies of other family members
 - Studies of specific platelet function abnormalities including: secretion studies, electron microscopy, flow cytometry
-

CAVEATS

- Most of these assays are affected by the blood collection technique. Blood should be obtained from a clean, atraumatic venipuncture to minimize activation of the coagulation factors or platelets prior to testing.
- Coagulation factors are labile and deteriorate after a few hours. Therefore if samples must be shipped to a specialty laboratory, the blood should be centrifuged (10,000 g x 10 minutes at 4°C), the plasma removed from the red cells and frozen immediately, then sent on dry ice to the laboratory doing the tests.
- Levels of VWF are affected by hormonal therapy including oral contraceptives, pregnancy and possibly by monthly changes in hormone levels.
- Levels of VWF and Factor VIII are affected by strenuous exercise, stress including recent surgery and inflammation. Because of these effects it may be necessary to test women with a positive history and equivocal laboratory results on more than one occasion.
- Levels of VWF vary with blood type; individuals with type O naturally have levels that are 25-30% lower than individuals with blood types A,B, or AB.
- Platelet function is affected by a variety of drugs including, but not limited to, salicylates, NSAIDs, antihistamines, and herbal therapies such as feverfew.
- Vitamin K dependent coagulation factors may be low because of vitamin K deficiency (producing a prolonged PT and/or APTT). Vitamin K deficiency can occur because of inadequate intake, malabsorption or inhibition by drugs.
- Some mild (Factor XI) coagulation factor deficiencies may not be identified by screening tests.

Desmopressin testing (DDAVP®):

- If a woman is found to have a hemostatic abnormality for which therapy with desmopressin is indicated (such as VWD type 1), it may be useful to confirm a response in the individual before planning to use this therapy.
- Laboratory studies pre- and 30 minutes post-desmopressin (intravenous):
 - Bleeding time/closure time
 - Factor VIII
 - VWF antigen
 - VWF functional assay

Medical treatment of menorrhagia in women with bleeding disorders

There is very good evidence that the quality of life of many women with bleeding disorders is diminished due to menorrhagia. Many effective medical strategies now exist to treat this problem. However, there is considerable variation in practice and prospective studies are needed to accurately define the relative place of each therapy. Management needs to be individualized and is best undertaken in a coordinated fashion by both hematologists and gynecologists. This approach should result in a substantial reduction in hysterectomies and a significant enhancement in the quality of life.

Menarche :

Excessive menstrual bleeding starting at menarche is a particularly frightening problem for adolescent girls with bleeding problems. This concern should be discussed ahead of time with the girl and her family to assure them that a variety of effective treatment options are available to intervene in this circumstance.

Treatment Options:

Hormonal Therapy

In many women, combination oral contraceptives are an effective and safe therapy for menorrhagia, reducing menstrual blood loss by approximately 50%¹⁵. These agents work, at least in part, through increasing the plasma levels of Factor VIII and VWF. The combination oral contraceptives are, of course, especially appropriate in women who also require effective contraception. More recently, another mode of chronic progestogen delivery has become available in the form of a levonorgestrel-releasing intrauterine device (Mirena[®])¹⁶. This system has been extensively evaluated in women on waiting lists for hysterectomy, and has been shown to reduce menstrual blood loss by between 74-97% and result in 64-82% of women subsequently canceling their hysterectomies¹⁷⁻¹⁹. A practical limitation to the use of this device is the fact that small uterine cavity size makes its use difficult in early adolescence.

Anti-fibrinolytic Agents

The antifibrinolytic drug, tranexamic acid, substantially reduces the fibrinolytic capacity of menstrual blood and, as a result, menstrual blood loss is reduced by approximately 50% on average²⁰. An advantage of this treatment is that it only needs to be taken at the time of the menstrual bleeding. The standard adult dose of tranexamic acid is 1 gm Q6H but limited experience with a single daily 4 gm dose has proven to be equally efficacious and well tolerated²¹. The only side effect, seen at all commonly, is mild nausea.

Desmopressin (DDAVP®)

Desmopressin has been used for approximately 20 years to treat patients with mild hemophilia A and VWD²². In addition, patients with platelet function disorders may also benefit from the use of this agent²³. The drug works through an interaction with V2 vasopressin receptors and causes a release of VWF from endothelial cell stores. Plasma Factor VIII levels also increase after desmopressin administration, most likely secondary to the increased VWF levels.

After a standard 0.3 µg/Kg (maximum dose 20 µg) intravenous dose of desmopressin, VWF and Factor VIII levels increase by 2 to 6-fold from baseline. Maximum levels of Factor VIII and VWF are found between 30-60 minutes after intravenous infusion and between 30-120 minutes after intranasal administration²⁴.

For the treatment of menorrhagia secondary to VWD, in carriers of hemophilia A or in patients with platelet dysfunction, administration of desmopressin by either the intranasal²⁵ or subcutaneous²⁶ routes is most practical. Desmopressin can be a very effective complement of anti-fibrinolytic therapy. The intranasal desmopressin spray (Octostim® Nasal Spray – concentration 1.5 mg/ml) is administered in a dose of 300 µg, achieved through one spray in each nostril. Each bottle of the spray contains sufficient material for 12 treatments and costs approximately \$380. The subcutaneous desmopressin dose (Octostim® injection) is 0.3 µg/kg. Desmopressin administration should begin when menstrual bleeding starts and can be repeated at 12-24 Hr intervals for the first two to three days of menstruation. Although tachyphylaxis has been reported with frequent repeat doses of desmopressin, a therapeutic response of approximately 70% of the initial increment is still usually achieved²⁷.

The side effects of desmopressin are usually mild and transient. Facial flushing is the most frequent accompaniment and minor changes in pulse and blood pressure can be observed. As a synthetic analogue of the natural antidiuretic hormone vasopressin, desmopressin has an antidiuretic effect that lasts for approximately 24 hours after the administration of the drug and thus, fluid intake should be limited to about 75% of normal to prevent the development of significant hyponatremia²⁸.

Pregnancy in patients with bleeding disorders

Pregnancy in patients with coagulation disorders is possible and not uncommon and management requires a multidisciplinary approach. Ideally, there should be an initial discussion between the future parents and the medical team before the pregnancy is planned. It is a good opportunity to complete investigation if necessary.

Discussion should include:

- 1) the risk of bleeding for the mother and the baby,
- 2) the proposed management during pregnancy, delivery and the postpartum and
- 3) the risk of having an affected baby and prenatal diagnosis if relevant.

The management of the pregnancy, delivery and postpartum will be reviewed for patients with VWD, carriers of hemophilia A and B and Factor XI deficiency. Prenatal diagnosis is beyond the scope of this review.

Physiological response expected in pregnancy in women with bleeding disorders

Factor VIII, Von Willebrand antigen and activity usually increase significantly during pregnancy in patients with type 1 VWD^{29,31} and in hemophilia A³² carriers and reach their maximum level between 29-35 weeks²⁹. In type 2 VWD, Factor VIII usually increases with persistence of the abnormal multimer pattern while factor correction is minimal in type 3^{29,35}. Women with type 2B VWD may develop worsening thrombocytopenia during pregnancy³⁵. Factor IX and XI levels usually do not change significantly during pregnancy^{8,31,32}. Thus, factors levels are not predictable during pregnancy and should always be tested during the third trimester. After delivery, factor levels return to baseline levels usually in 7-10 days but sometimes more rapidly^{34,36}.

Management of the pregnancy

During pregnancy

Bleeding is rare during pregnancy. In preparation for the delivery factor levels should be measured during the third trimester (32-34 weeks). If a diagnostic (such as amniocentesis) or therapeutic procedure is planned during the pregnancy, factor levels should be measured prior to the procedure. A factor level of 0.5 U/ml is generally considered adequate for diagnostic techniques as well as for delivery^{8,31,37}. If the mother is a hemophilia carrier determination of the sex of the baby by ultrasound is recommended because the information will be useful to the obstetrician at the time of delivery. When the factor levels results are available in the third trimester, final recommendations for the delivery should be discussed with the patient and written in the chart. In addition, a copy of the recommendations should be given to the patient who will give it to the physician who will admit her in the delivery room. It is important that women with bleeding disorders deliver in an hospital where there is access to hematologists, obstetricians and pediatric consultants.

Labor and delivery

While it would be ideal to have factor or VWF levels done on admission, this is often impractical and there should be very little variation between the levels measured during the third trimester and those performed on admission. The factor level considered adequate for vaginal delivery and cesarean is 0.5 U/ml^{1,8,37}.

During delivery it is important to minimize maternal genital tract or perineal lacerations.

The risk of bleeding in an affected fetus is small and a cesarean is not recommended in all patients^{8,38}. However, vacuum extraction, forceps and scalp fetal electrodes are not recommended³⁸. Delivery should be non-traumatic and cesarean should be considered if labor does not progress normally.

Epidural anesthesia

Epidural anesthesia is always controversial in the presence of a coagulation defect because a hematoma may occur if a vessel is punctured in the spinal canal and cause permanent neurological damage. There are case reports of patients with type 1 VWD and Factor XI deficiency who had epidural anesthesia without any complications but there are no large series available^{8,31,39,40}. It is generally accepted that there is no contraindication if coagulation is normal^{8,37}. Factor levels performed late during the third trimester are useful to make a decision. However, there is no consensus and decision should be made individually after discussion with the patient before delivery and clearly indicated in the chart.

Post partum

In the general population, the risk of early postpartum hemorrhage (during the first 24 hours after delivery) is 4-5%. This risk is clearly increased to 16 to 22% in patients with VWD, Factor XI deficiency and hemophilia carriers^{30,31,37,41}. The risk of late postpartum hemorrhage is also increased to 11-25% in women with coagulation disorders compared to less than 1% in the general population^{30,31,37}. The severity of late postpartum hemorrhage varies depending on how rapidly factor levels return to normal. It is generally recommended to keep factor level above 0.5 U/ml for 3-4 days after a vaginal delivery and 4-5 days after a cesarean section^{37,42}. Women at risk of late postpartum hemorrhage should be instructed about possible excessive bleeding and should be seen in a follow up visit 2 weeks post partum.

Neonate

If the baby is at risk of being affected, blood samples should be taken of cord blood. In some cases, factor levels are not diagnostic at birth but the result usually gives a good idea of whether the child is affected and provides baseline levels in case an intervention is required. If the factor levels are not informative, they should be repeated at a later time.

Intra-muscular injections and circumcision should be avoided in neonates who have a coagulation disorders or in whom the factor level is unknown. Vitamin K should be given orally or SC with 10 minutes of pressure³⁷. It is usually recommended to perform trans-fontanel ultrasound soon after birth if the baby is severely

affected. It is not clear that a baby with severe coagulopathy should stay longer in the hospital. If the baby is discharged early from the hospital, he should probably be seen for follow-up at 10-14 days. If the neonate is affected, he should be registered at the hemophilia center and the usual counseling given.

If treatment is required what is the choice ?

Labor and delivery

There are very few published data on the use of desmopressin during pregnancy⁴³ but there are some concerns that desmopressin causes uterine contraction with premature labor, intrauterine growth retardation and hyponatremia. For these reasons, it is advisable to be cautious about the use of desmopressin during pregnancy. However, once the cord is clamped, desmopressin can be used if necessary. It is also probably reasonable to use desmopressin immediately before a cesarean. Desmopressin is not contraindicated during lactation.

For patients with severe VWD, Humate-P is the treatment of choice. Desmopressin has no effect on Factor IX. For IX carriers, recombinant IX is available and would be the first choice of treatment if required. Many patients with Factor XI deficiency do not bleed and if the deficiency is mild and there is no history of significant bleeding, treatment can usually be withheld. If treatment is required Factor XI concentrate is available but associated with thrombosis. There is limited but successful experience with desmopressin in patients with Factor XI deficiency⁴⁴. SD plasma is the alternative.

Post partum

If late postpartum hemorrhage occurs tranexamic acid and oral contraceptives are useful. Prophylactic oral contraceptives started immediately after delivery and continued for one month postpartum may be considered in some patients in order to reduce postpartum hemorrhage. Treatment should be discussed with the obstetrician. The risk of thrombosis might be a concern if antifibrinolytic agents are used in the postpartum but the risk is probably reasonable in patient who do not have other risk factors.

In patients with bleeding disorders who first present during pregnancy it is important to obtain baseline factor levels a few months after delivery and lactation.

References

1. Kouides PA. Females with von Willebrand disease: 72 years as the silent majority. *Haemophilia*. 1998;4:665-676.
2. Dilley A, Crudder S. von Willebrand Disease in women: the need for recognition and understanding. *J Womens Health Gend Based Med*. 1999;8:443-445.
3. Nilsson IM. Commentary to Erik von Willebrand's original paper from 1926 'Hereditar pseudohefili'. *Haemophilia*. 1999;5:220-221.
4. Ragni MV, Bontempo FA, Hassett AC. von Willebrand disease and bleeding in women. *Haemophilia*. 1999;5:313-317.
5. Kouides PA, Phatak PD, Burkart P, et al. Gynaecological and obstetrical morbidity in women with type I von Willebrand disease: results of a patient survey. *Haemophilia*. 2000;6:643-648.
6. Kadir RA, Economides DL, Sabin CA, Pollard D, Lee CA. Assessment of menstrual blood loss and gynaecological problems in patients with inherited bleeding disorders. *Haemophilia*. 1999;5:40-48.
7. Lak M, Peyvandi F, Mannucci PM. Clinical manifestations and complications of childbirth and replacement therapy in 385 Iranian patients with type 3 von Willebrand disease. *Br J Haematol*. 2000;111:1236-1239.
8. Kadir RA, Economides DL, Lee CA. Factor XI deficiency in women. *Am J Hematol*. 1999;60:48-54.
9. Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA. Frequency of inherited bleeding disorders in women with menorrhagia. *Lancet*. 1998;351:485-489.
10. Edlund M, Blomback M, von Schoultz B, Andersson O. On the value of menorrhagia as a predictor for coagulation disorders. *Am J Hematol*. 1996;53:234-238.
11. Dilley A, Drews C, Miller C, et al. von Willebrand disease and other inherited bleeding disorders in women with diagnosed menorrhagia. *Obstet Gynecol*. 2001;97:630-636.
12. Kadir RA, Sabin CA, Pollard D, Lee CA, Economides DL. Quality of life during menstruation in patients with inherited bleeding disorders. *Haemophilia*. 1998;4:836-841.
13. Bradlow J, Coulter A, Brooks P. Patterns of referral. Health Services Research Unit. University of Orford. 1992
14. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol*. 1990;97:734-739.

15. Irvine GA, Cameron IT. Medical management of dysfunctional uterine bleeding. *Baillieres Best Pract Res Clin Obstet Gynaecol.* 1999;13:189-202.
16. Barrington JW, Bowen-Simpkins P. The levonorgestrel intrauterine system in the management of menorrhagia. *Br J Obstet Gynaecol.* 1997;104:614-616.
17. Lahteenmaki P, Haukkamaa M, Puolakka J, et al. Open randomised study of use of levonorgestrel releasing intrauterine system as alternative to hysterectomy. *BMJ.* 1998;316:1122-1126.
18. Lethaby AE, Cooke I, Rees M. Progesterone/progestogen releasing intrauterine systems versus either placebo or any other medication for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2000;CD002126.
19. Irvine GA, Campbell-Brown MB, Lumsden MA, Heikkila A, Walker JJ, Cameron IT. Randomised comparative trial of the levonorgestrel intrauterine system and norethisterone for treatment of idiopathic menorrhagia. *Br J Obstet Gynaecol.* 1998;105:592-598.
20. Lethaby A, Farquhar C, Cooke I. Antifibrinolytics for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2000;CD000249.
21. Ong YL, Hull DR, Mayne EE. Menorrhagia in von Willebrand disease successfully treated with single daily dose tranexamic acid. *Haemophilia.* 1998;4:63-65.
22. Mannucci PM. Desmopressin: A nontransfusional hemostatic agent. *Annu Rev Med.* 1990;41:55-64.
23. DiMichele DM, Hathaway WE. Use of desmopressin in inherited and acquired platelet dysfunction. *Am J Hematol.* 1990;33:39-45.
24. Lethagen S, Harris AS, Sjorin E, Nilsson IM. Intranasal and intravenous administration of desmopressin: effect on F VIII/VWF, pharmacokinetics and reproducibility. *Thromb Haemost.* 1987;58:1033-1036.
25. Lethagen S, Ragnarson TG. Self-treatment with desmopressin intranasal spray in patients with bleeding disorders: effect on bleeding symptoms and socioeconomic factors. *Ann Hematol.* 1993;66:257-260.
26. Rodeghiero F, Castaman G, Mannucci PM. Prospective multicenter study on subcutaneous concentrated desmopressin for home treatment of patients with von Willebrand disease and mild or moderate hemophilia A. *Thromb Haemost.* 1996;76:692-696.
27. Mannucci PM, Bettega D, Cattaneo M. Patterns of development of tachyphylaxis in patients with haemophilia and von Willebrand disease after repeated doses of desmopressin (desmopressin). *Br J Haematol.* 1992;82:87-93.
28. Smith TJ, Gill JC, Ambruso DR, Hathaway WE. Hyponatremia and seizures in young children given desmopressin. *Am J Hematol.* 1989;31:199-202.
29. Chediak JR, Alban GM, Maxey B. von Willebrand's disease and pregnancy: Management during delivery and outcome of offspring. *Am J Obstet Gynecol* 1986;155:618-624.

30. Ramsahoye BH, Davies SV, Dasani H, Pearson JF. Obstetric management in von Willebrand's disease: a report of 24 pregnancies and a review of the literature. *Hemophilia* 1995;1:140-144
31. Kadir RA, Lee CA, Sabin CA, Pollard D, Economides DL. Pregnancy in women with von Willebrand's disease or Factor XI deficiency. *Br J Obstet Gynaecol* 1998;105:314-321.
32. Greer IA, Lowe GDO, Walker JJ, Forbes CD. Haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies. *Br J Obstet Gynecol* 1991;98:909-918.
33. Conti M, Mari D, Conti E, Muggiasca ML, Mannucci PM. Pregnancy in women with different types of von Willebrand disease. *Obstet Gynecol* 1986;68:282-285.
34. Hanna W, McCarroll D, McDonald T et al. Variant von Willebrand's disease and pregnancy. *Blood* 1981;58:873-879.
35. Rick ME, Williams SB, Sacher RA, McKeown LP. Thrombocytopenia associated with pregnancy in a patient with type IIB von Willebrand's disease. *Blood* 1987;69:786-789
36. Noller KL, Bowie EJW, Kempers RD, Owen F, Owen CA. Von Willebrand's disease in pregnancy. *Obstet Gynecol* 1973;41:865-872.
37. Kadir RA. Women and inherited bleeding disorders: Pregnancy and delivery. *Seminars in Hematology* 1999;36:28-35.
38. Ljung R, Lindgren A-C, Petrini P, Tengborn L. Normal vaginal delivery is to be recommended for haemophilia carrier gravidae. *Acta Paediatr* 1994;83:609-611.
39. Milaskiewicz RM, Holdcroft A, Letsky E. Epidural anaesthesia and von Willebrand's disease. *Anaesthesia* 1990;45:462-464
40. Cohen S, Daitch JS, Amar D, Goldiner PL. Epidural analgesia for labor and delivery in a patient with von Willebrand's disease. *Regional Anesth* 1989;14:95-97
41. Kadir RA, Economides DL, Braithwaite J et al. The obstetric experience of carriers of haemophilia. *Br J Obstet Gynaecol* 1997;104:803-810.
42. Walker ID, Walker JJ, Colvin BT, Letsky EA, Rivers R, Stevens R. Investigation and management of haemorrhagic disorders in pregnancy. *J Clin Pathol* 1994;47:100-108.
43. Mannucci PM. Treatment of von Willebrand disease. *Thromb Haemost* 2001;80:149-53.
44. Castaman G, Ruggeri M, Rodeghiero F. Clinical usefulness of desmopressin for prevention of surgical bleeding in patients with symptomatic heterozygous Factor XI deficiency. *Br J Haematol* 1996;94:168-170.

Appendix 1

EVALUATION OF YOUR NEXT MENSTRUAL PERIOD:

Please complete the following questionnaire during your next menstrual period. In order to assure reliable results, we would ask you to inscribe on a daily basis the information concerning your menstrual period in the tables which follow, for each pad or tampon used.

Pads:

Brand name of pad: _____

Absorption capacity: (Check the word which best describes the type of pad)

Light: _____

Regular: _____

Heavy: _____

Extra heavy: _____

Tampons:

Brand name of tampons: _____

Absorption capacity: (Check the word which best describes the type of tampon)

Light: _____







Regular: _____

Heavy: _____

Extra heavy: _____

For each day of your menstrual period, from days 1 to 12, check it off (/), in the appropriate case, indicating the day of menstruation, each time you change a pad and/or tampon. For example, if on day “one” you have used 2 lightly soaked pads, 5 moderately soaked pads and 4 very soaked tampons, one should find, under day “one”, two slashed (/) vis a vis the picture indicating a lightly soaked pad, five slashed (/////) vis a vis the picture indicating a moderately soaked pads and four slashed (////) vis a vis the picture indicating a heavily soaked tampon. If you use both a pad and tampon simultaneously, write in your slashes vis a vis the picture illustrating pads and tampons. If your menstrual period lasts more than 12 days, indicate the number of days under the table but don’t add days to the table.

MONTH _____

DAYS	1	2	3	4	5	6	7	8	9	10	11	12
DATES												
PADS												
Lightly soaked 												
Moderately soaked 												
Heavily soaked 												
TAMPONS												
Lightly soaked 												
Moderately soaked 												
Heavily soaked 												
Clots 1cm or less												
Clots More than 1cm												
Blood flowing outside the pad or tampon												

(Table inspired by J.M. Higham et al. Br. J. Obstet. Gynecol. 1990;97:734-9)

Total number of days of menstrual period: _____

Menstrual score: _____

Appendix 2

Introduction:

In preparation for your next appointment in the women with bleeding disorders' clinic, we would ask you to fill in this questionnaire, to the best of your knowledge. The answers that you give will be used to decide the precise nature of your coagulation problem and will allow, if need be, to make the most judicious possible supplementary investigation necessary for a precise diagnosis and for satisfactory treatment. When you come for your appointment you must give this duly completed questionnaire to the nurse in charge of the program. This document will then be added to your medical file and will be treated with the same rules of confidentiality as other information therein.

If you have already had an investigation for another hemorrhagic problem in another hospital, it would be useful to bring the results of this investigation with you. These results can be obtained by contacting the archival services of the hospital where the investigation was done.

If you have any difficulties completing this questionnaire, don't hesitate to contact the nurse at:

Doctor to whom you wish us to send the results of this investigation:

Name: _____

Address: _____

Telephone: _____

Personal history:

■ General:

- Do you have a tendency to have bruises?
Not at all Very little A bit A lot Very much
- Do you have a tendency to bleed from the gums when you brush your teeth?
Not at all Very little A bit A lot Very much
- Do you use a razor to shave?
No
Yes If yes:
Do you have a tendency to bleed?
Not at all Very little A bit A lot Very much
- Do you have a tendency to have nosebleeds with no apparent reason?
Not at all Very little A bit A lot Very much
- Have you already had an abnormal loss of blood necessitating a medical consultation following an injury, a tooth extraction, surgery or curettage?
No
Yes If yes:
How old were you? _____
What was the problem? _____

What was the treatment? _____

- Has a doctor already told you that you have a blood coagulation problem?
No
Yes If yes:
How old were you? _____
What was the diagnosis? _____
What treatment did you receive? _____
- Do you take medication on a regular basis?
No
Yes If yes:
List the names of the medication you have taken in the last month:

■ Personal gynecological history

- At what age did your menstrual periods begin? _____
- At what age did you consider that your menstrual periods are abnormal? _____
- At what age did you consult a doctor for the first time for abnormal menstrual bleeding? _____
- In how many days does your menstrual cycle reoccur? _____
- How many days does the bleeding last? _____
- Do you bleed between your menstrual periods?
 No
 Yes If yes:
 Very rarely Rarely Often Very often Always
- Do you have clots during your menstruation?
 No
 Yes If yes:
 Very rarely Rarely Often Very often Always
- Do you stain your clothing during your menstruation?
 Very rarely Rarely Often Very often Always
- Do you stain your bed during your menstruation?
 Very rarely Rarely Often Very often Always
- Do you have pain during your menstruation?
 Not at all Very little A bit A lot Very much
- Do you take medicine to alleviate your menstrual pain?
 Never Rarely Often Very often Always
 If yes: What medication do you take?

- During the last month, have you missed school or work because of your menstruation?
 No
 Yes
 If yes: How many days? _____
- Does your menstrual period interfere with your social life?
 Not at all Very little A bit A lot Very much
- Does your menstrual period interfere with your sex life?
 Not at all Very little A bit A lot Very much

- Have you ever taken contraceptives (the Pill)?
No
Yes If yes:
For contraception
To regularize your cycle
To diminish your bleeding
- Did the contraceptives:
Increase your menstrual period
Diminish your menstrual period
Change nothing in your menstrual period

■ Personal obstetrical history

- Have you ever tried to get pregnant?
No
Yes
- How many times have you been pregnant? _____
- In general, for the majority of your pregnancies, how much time passed, on average, between the time you decided to get pregnant and the moment you became pregnant?
Less than 3 months
Between 3 and 6 months
Between 6 et 12 months
More than 12 months
- How many voluntary interruption of pregnancies (abortions) have you had? _____
- How many spontaneous abortions (miscarriages) have you had? _____
Indicate for each spontaneous abortion, the number of weeks of pregnancy at the time of the miscarriage: _____
- How many times have you given birth? _____
Vaginal birth: _____
Cesarean section: _____
- Did your doctor tell you that you bled abnormally after one or more of your childbirth?
No
Yes
You bled abnormally at:
How many vaginal births? _____
How many cesarean sections? _____
- Have you needed a blood transfusion for a hemorrhage associated with childbirth?
No
Yes

■ Familial history

- Do you have brothers? Yes No Sisters? Yes No

If yes:

How many living brothers do you have? _____

How many living sisters do you have? _____

Have you ever lost a brother or sister because of bleeding?

No

Yes

Details: _____

- Do you have sisters?

No

Yes

If yes:

Do you have sisters with abnormal menstrual periods?

No

Yes

If yes:

How many? _____

Illness known to explain their abnormal menstrual periods? _____

- Does your mother have a history of abnormal menstrual periods?

I don't know

No

Yes If yes

Illness known to explain their abnormal menstrual periods? _____

- Do you have someone in your immediate or close family who is known to have a hereditary (from birth) hemorrhagic problem?

I don't know

No

Yes If yes

What is your relation to this person? _____

What is the name of the hereditary hemorrhagic problem? _____

Supplementary information obtained from the questionnaire:

Medical opinion of the history:

EVALUATION OF HEMOSTASIS

This part of your file will be completed by the medical personnel

				Normal values	Results
Hemoglobin	(Y	M	D)	_____	_____
Hematocrit	(Y	M	D)	_____	_____
Platelets	(Y	M	D)	_____	_____
Blood type ABO					_____
Thrombin time	(Y	M	D)	_____	_____
INR	(Y	M	D)	_____	_____
APTT	(Y	M	D)	_____	_____
Fibrinogen	(Y	M	D)	_____	_____
Factor VIII	(Y	M	D)	_____	_____
VWF: Ag	(Y	M	D)	_____	_____
VWF functional assay	(Y	M	D)	_____	_____
PFA-100(Epi)	(Y	M	D)	_____	_____
PFA-100(ADP)	(Y	M	D)	_____	_____
Bleeding time	(Y	M	D)	_____	_____
_____	(Y	M	D)	_____	_____
_____	(Y	M	D)	_____	_____
_____	(Y	M	D)	_____	_____
_____	(Y	M	D)	_____	_____

Comments on the overall clinical and biological information:

Signed: _____ Y _____ M _____ D _____

Appendix 3

Contact Information:

ASSOCIATION OF HEMOPHILIA CLINIC DIRECTORS OF CANADA (AHCDC)

Mission Statement:

The goal of the AHCDC is to ensure excellent care for persons with congenital bleeding disorders in Canada through clinical services, research and education.

Association of Hemophilia Clinic Directors of Canada
Suite 2-008, 38 Shuter Street, Toronto, Ontario M5B 1A6
Tel: (416) 864-5042 – Fax: (416) 864-5251
E-mail: vogela@smh.toronto.on.ca



Canadian Hemophilia Society
We're all related by blood.

Mission:

The Canadian Hemophilia Society (CHS) exists to improve the quality of life for all persons with hemophilia and other inherited bleeding disorders and to find a cure.

Educational Publications about VWD (to order contact CHS)

- VWD... Your Questions Answered – an information booklet about VWD – (16 pages)
- All About von Willebrand Disease – a comprehensive guidebook for people with VWD and their families – (86 pages)
- Desmopressin – DDAVP, Octostim, Octostim Spray and Stimite – a guide for patients and caregivers (pamphlet)
- Amicar and Cyklokapron – a guide for patients and caregivers (pamphlet)
- Clinical Focus: Bleeding Disorders in Women – a guide for physicians (April, 2002 insert in Medical Post)

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